Transport Phenomena in the Lymphatic System

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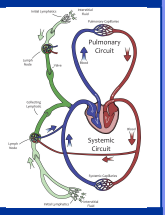
Background

Motivations

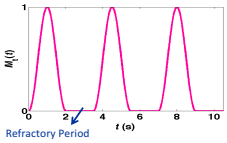
- Fluid and protein balance
- All deadliest forms of cancer spread via lymphatics
- 90% of cancer deaths are due to secondary tumors
- All immune responses rely on lymph flow and chemokine concentration gradients
- Pathologies such as lymphoedema with no cure
- A well-developed model can improve our understanding of the system behavior



Pumping Model Parameters

Active vessel contraction (Lymphatic Muscle Cell contraction)

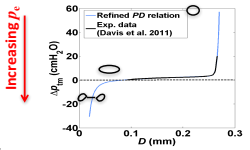
Refractory period:



Passive behaviour of the vessel

Pressure-Diameter relationship:

Transmural pressure: $\Delta p_{tm} = p_m - p_e$



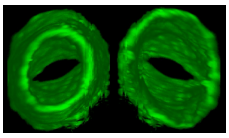
Lumped Parameter Model:

Equations of conservation of mass
conservation of momentum
vessel wall force balance

→ Non-linear ODE for diameter
Solved computationally (MATLAB)

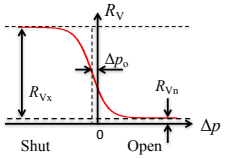
Valve Behavior:

flow

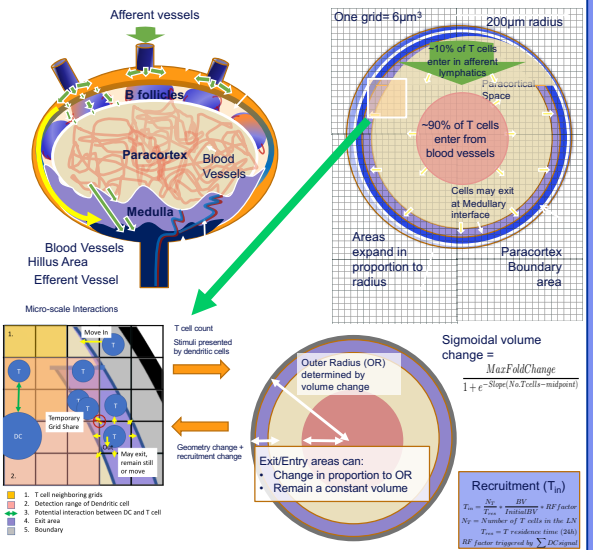


pressure difference across the valve

Δp = Upstream – Downstream

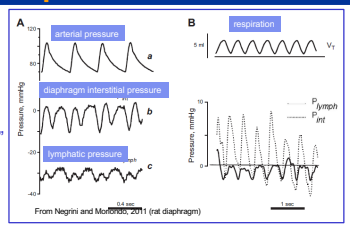


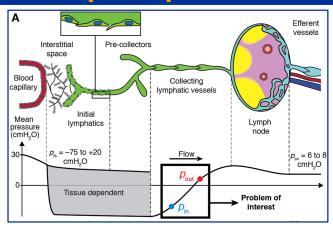
Agent-Based Model of Immune Cell Actions



Lymphatics pump fluid from tissues with subatmospheric pressures

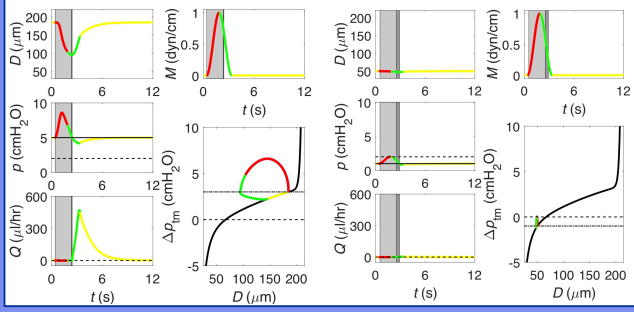
- Many of the body's tissues exhibit subatmospheric interstitial pressures
- Lymphatics pump "up" to subclavian vein by squeezing
- How is fluid "sucked in?"



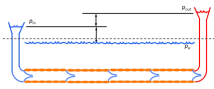


Positive Transmural Pressure

Negative Transmural Pressure



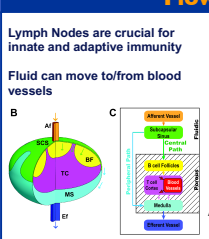
- The key: Diastolic filling
- Requires positive transmural pressure or vessel tethering
- Pumping is unchanged when three relevant pressures are adjusted in concert



Flow and Chemokine Gradients in Lymph Nodes

Lymph Nodes are crucial for innate and adaptive immunity

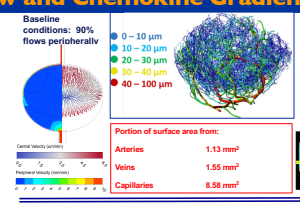
Fluid can move to/from blood vessels



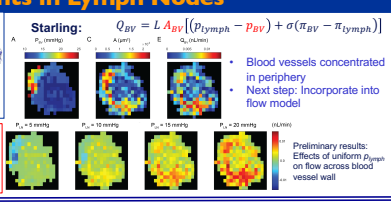
Chemokines are small (10-20 kDa) cytokines for immune cells

CCL19 and CCL21 (ligands to CCR7 and ACKR4) instigate dendritic cell and macrophage migration in periphery and in nodes

Cells follow concentration gradients

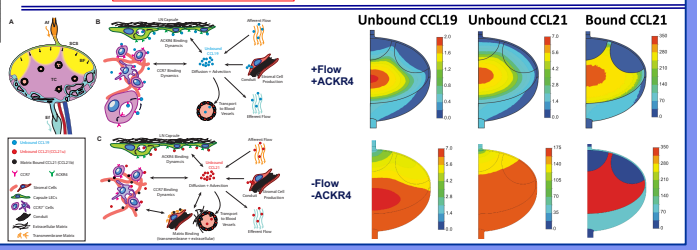


Starling: $Q_{BV} = L\,A_{BV}\left[(p_{lymph} - p_{BV}) + \sigma(\pi_{BV} - \pi_{lymph})\right]$



- Blood vessels concentrated in periphery
- Next step: Incorporate into flow model

Preliminary results: Effects of uniform p_{lymph} on flow across blood vessel wall



ABM Results: Lymph node swelling facilitates adaptive immunity

Antigen Presenting Dendritic Cell

- Present MHCI & II as decaying stimuli
- Appear gradually over 2 days

T Cell ~10⁶ per LN

- 70% Helper
- 30% Cytotoxic
- Random walk at 12μm min⁻¹ in 10000 TCs recognize antigen
- TCs interact with DCs and gain stimulation that decays with time.

SIGNAL INTEGRATION & SIGMOIDAL PROBABILITY THRESHOLDS

- Determine TC progress through..
  - Activation
  - Proliferation
  - Early Differentiation to Effector T Cells
  - Late Differentiation Effector + Memory Cells

T CELL EXIT

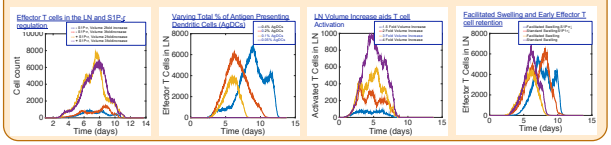
A fixed egress parameter & Sphingosine-1-Phosphate ($S1P_1$) receptor expression determine exit probability.
Activated TCs down-regulate $S1P_1r$.

Figure 1: Blocking activated TCs $S1P_1r$ down-regulation dampens effector cell response regardless of maximum volume increase.

Figure 2: Varying stimuli strength via DC input linearly affects response, but below a certain threshold, response is abolished completely.

Figure 3: Increasing maximum possible LN volume can aid effector cell production by increasing T cell activation.

Figure 4: Facilitating swelling inhibits response. Retaining early effector TCs via $S1P_1r$ downregulation aids TC effector response in all cases.



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